REMARKS

The newly claimed invention is directed to methods of treating refractory tumors, (Specification p. 5, ll. 18-20), which have failed or been resistant to treatment. (Specification p. 5, ll. 22-23.) In the present inventive methods, a human patient is treated by administration of an antagonist of EGFR. (Specification p. 17, ll. 19-21.)

Amendments

The specification has been amended to correct inadvertent typographical errors and to literally include material that had been incorporated by reference. Claims 1-35 have been deleted and new claims 36-72 have been added. The new claims have been added to more particularly point out and distinctly claim the present invention. The amendments to the specification and new claims and abstract are fully supported by the specification as originally filed. Accordingly, no new matter has been added. It should be noted, however, that the new claims recite therapy using an EGFR antagonist alone. Claims reciting therapy using an EGFR antagonist in combination with an antineoplastic agent are being pursued in the parent application.

Attached hereto are a copy of a version of the amendments with markings to show the changes made and, for the convenience of the Examiner, a copy of the pending claims upon entry of the present amendments.

Outstanding Issues

The present application is a continuation of Application No. 09/374,028. In the parent '028 application, an Office Action dated October 24, 2000, was outstanding. In this Office Action, the Office had issued the following rejections: (i) claims 1-33 were rejected under 35

U.S.C. § 112, ¶ 2 as unclear (ii) claims 1-33 were rejected under 35 U.S.C. § 112, ¶ 1 as not enabled by the specification; and (iii) claims 1-33 were rejected under 35 U.S.C. § 103(a) as obvious over Baselga et al., *Breast Cancer Res.*, 29: 127-138 (1994) alone (claims 1-3, 6-9, and 22-23) or in light of Han et al., *Oncol. Res.*, 9: 581-87 (1997) (claims 1-9 and 22-33) or U.S. Patent No. 4,863,902 (Amagase et al.) (claims 1-3 and 6-33).

Section 112, Second Paragraph Issues

In the Office Action dated October 24, 2000, claims 1-33 were rejected under 35 U.S.C. § 112, ¶ 2 for unclear recitation of "refractory tumor". The new claims specify the refractory tumors of the present invention as having failed or been resistant to treatment, i.e., the refractory tumors have failed or been resistant to first line treatment.

In the Office Action dated October 24, 2000, claims 1-33 were also rejected under 35 U.S.C. § 112, ¶ 2, for unclear recitation of "effective amount". The new claims recite that administration of the EGFR antagonist is effective to inhibit growth of the refractory tumor. Such inhibition is sufficient to prevent or reduce the progession, i.e., growth, invasion and/or metastasis, of the refractory tumor.

Section 112, First Paragraph Issues

In the Office Action dated October 24, 2000, claims 1-33 were rejected under 35 U.S.C. § 112, ¶ 1 as not enabled by the specification. According to the Office, there is no enablement for treatment of all tumors with all EGFR antagonists either alone or in combination with a chemotherapeutic agent. The new claims recite that the type of tumor encompassed by the present invention has failed or been resistant to treatment. Furthermore, the present claims are directed to monotherapy, rather than combination therapy involving an

antineoplastic agent. It appears that, in light of these new claims, the only remaining issue may be directed to the scope of the term EGFR antagonist.

An EGFR antagonist, in the context of the present invention, is any substance that inhibits stimulation of EGFR. (Specification p. 7, ll. 3-5.) Binding of a ligand, e.g., epidermal growth factor (EGF) or transforming growth factor-α (TGF-α), to an external, extracellular domain of EGFR stimulates receptor dimerization, autophosphorylation of EGFR, activation of the receptor's internal, cytoplasmic tyrosine kinase domain, and initiation of multiple signal transduction and transactivation pathways involved in regulation of DNA synthesis and cell division. Accordingly, an EGFR antagonist is any substance that inhibits and/or disrupts one or more of these activities normally associated with EGFR stimulation.

Examples of EGFR antagonists include, for example, biological molecules, such as antibodies specific for EGFR, and small molecules that inhibit EGFR. (Specification p. 7, ll. 20-23, p. 8, ll. 3-4.) Aside from the many EGFR antagonists already known in the art, one skilled would be able to determine, using assays described, for example, in the specification at page 7, lines 14-19, whether or not new substances function as EGFR antagonists.

A known biological molecule EGFR antagonist is ERBITUX™ (IMC-C225), which is a chimeric (human/mouse) monoclonal antibody specific for EGFR. (Specification p. 12, line 12 – p. 14, line 9.) The monoclonal antibody ERBITUX™ specifically binds EGFR and blocks binding of a ligand, e.g., EGF. In addition, or alternatively, the monoclonal antibody ERBITUX™ may promote internalization of the receptor-antibody complex, preventing further stimulation of the receptor by its ligand or any other mechanism.

Another example of a biological molecule EGFR antagonist is ABX-EGF, which is a fully human IgG_2 monoclonal antibody specific for EGFR. ABX-EGF binds EGFR with high specificity, blocking binding of EGFR to both of its ligands, EGF and TGF-α. See, e.g.,

Figlin et al., Abstract 1102 presented at the 37th Annual Meeting of ASCO, San Francisco, CA, 12-15 May 2001. The sequence and characterization of ABX-EGF, which was formerly known as clone E7.6.3, is disclosed in U.S. Patent No. 6,235,883 (Abgenix, Inc.) at col. 28, line 62 through col. 29, line 36; Fig. 29-34.[1]

One example of a small molecule EGFR antagonist is IRESSA™ (ZD1939), which is a quinozaline derivative that functions as an ATP-mimetic to inhibit EGFR. *See* U.S. Patent No. 5,616,582 (Zeneca Limited); WO 96/33980 (Zeneca Limited) at p. 4; *see also*, Rowinsky et al., Abstract 5 presented at the 37th Annual Meeting of ASCO, San Francisco, CA, 12-15 May 2001; Anido et al., Abstract 1712 presented at the 37th Annual Meeting of ASCO, San Francisco, CA, 12-15 May 2001.

TARCEVA™ is another example of a small molecule EGFR antagonist. TARCEVA™ (OSI-774) is a 4-(substitutedphenylamino)quinozaline derivative [6,7-Bis(2-methoxy-ethoxy)-quinazolin-4-yl]- (3-ethynyl-phenyl)amine hydrochloride] EGFR inhibitor, which is described in WO 96/30347 (Pfizer Inc.) at, for example, page 2, line 12 through page 4, line 34 and page 19, lines 14-17. *See also* Moyer et al., *Cancer Res.*, 57: 4838-48 (1997); Pollack et al., *J. Pharmacol.*, 291: 739-48 (1999). TARCEVA™ may function by inhibiting phosphorylation of EGFR and its downstream PI3/Akt and MAP (mitogen activated protein) kinase signal transduction pathways resulting in p27-mediated cell-cycle arrest. *See* Hidalgo et al., Abstract 281 presented at the 37th Annual Meeting of ASCO, San Francisco, CA, 12-15 May 2001.

Many other small molecules are known to inhibit EGFR. Some examples of small molecule EGFR antagonists are described in the specification at page 14, line 24 through

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[1] See Yang et al., *Critical Rev. Oncol./Hematol.*, 38(1): 17-23, 2001.

page 16, line 7 and in WO 97/30034 (Zeneca Limited), WO 97/42187 (Zeneca Limited), and WO 98/33798 (Warner Lambert Company). Examples of specific small molecule EGFR antagonists include CI-1033, which is a quinozaline (N-[4-(3-chloro-4-fluoro-phenylamino)-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-yl]-acrylamide) inhibitor of tyrosine kinases, particularly EGFR and is described in WO 00/31048 (Warner-Lambert Company) at page 8, lines 22-6; PKI166, which is a pyrrolopyrimidine inhibitor of EGFR and is described in WO 97/27199 (Novartis AG) at pages 10-12; GW2016, which is an inhibitor of EGFR and HER2; and EκB569.

EGFR antagonists have been shown to be effective when administered to treat refractory tumors. For example, IRESSA™ has been shown to be effective as a second- or third-line treatment when administered orally as a single agent on a once a day dosing schedule to treat human patients with refractory (having failed at least one round of platinum-based therapy) NSCLC. *See* Baselga et al., Abstract presented at the 12th AACR-NCI-EORTC International Conference, Miami, FL, 2001; *see also* Negoro et al., Abstract 1292 presented at the 37th Annual ASCO Meeting, San Francisco, CA, May 12-15, 2001. Another small molecule EGFR antagonist, TARCEVA™ (150 mg) has been shown to be effective in a phase II trial for administration orally as a single agent on a once-a-day dosing schedule to treat human patients with refractory (having failed at least one round of platinum-based chemotherapy), EGFR-positive NSCLC. *See* Bonomi et al., Abstract 386 presented at the 11th NCI-EORTC-AACR Symposium, Amsterdam, The Netherlands, November 7-10, 2000. TARCEVA™ has also been shown to be effective in a phase II trial for administration to human patients with advanced ovarian cancer refractory to treatment with a taxane and/or platinum agent using similar dosing as the NSCLC trial. *See* Finkler et al., Abstract 831 presented at the 37th Annual ASCO Meeting, San Francisco, CA, May 12-15, 2001.

Moreover, according to Abgenix, Inc., ABX-EGF has been shown to be effective in a phase I study of 28 patients with advanced, refractory cancer (kidney, prostate, pancreatic, NSCLC, colorectory, and esophageal). *See* Figlin et al., Abstract 1102 presented at the 37th Annual ASCO Meeting, San Francisco, CA, May 12-15, 2001).

Obviousness Issues

Claims 1-3, 6-9 and 22-23 were rejected under 35 U.S.C. § 103(a) as obvious over Baselga et al. In addition, claims 1-9 and 22-33 were rejected under 35 U.S.C. § 103(a) as obvious over Baselga et al. in light of Han et al. Finally, claims 1-3 and 6-33 were rejected under 35 U.S.C. § 103(a) as obvious over Baselga et al. in light of Amagase et al. According to the Office, Baselga et al. teaches a method of inhibiting tumor growth in humans with an effective amount of a monoclonal antibody that inhibits EGFR phosphorylation, including combination therapy with a chemotherapeutic agent.

None of the references cited teach or suggest refractory tumors that have failed or been resistant to treatment. As discussed during the Examiner Interview, and set forth the Interview Summary, the new claims are not obvious over Baselga et al. in light of either Han et al. or Amagase et al.

CONCLUSION

Applicants believe that the present application is in condition for allowance, and respectfully request that the Office pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

The Office is authorized to charge any fees that may be necessary for consideration of this paper to Kenyon & Kenyon Deposit Account No. 11-0600.

Respectfully submitted,

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Dated: December 21, 2001

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

At page 7, ll. 7-11:

The growth of refractory tumors is sufficiently inhibited in the patient to prevent or reduce the progression of the cancer (i.e. growth, invasiveness, metastasis, and/or recurrence). The EGFR antagonists of the present invention can be cytostatic or inhibit the growth of the refractory tumor. Preferably, the EGFR [ERGR] antagonist is cytolytic or destroys the tumor.

At page 7, ll. 20-25:

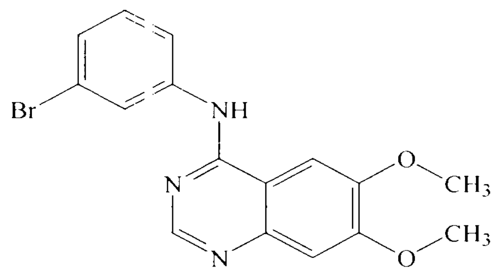
EGFR/HER1 antagonists include biological molecules and [or] small molecules. Biological molecules include all lipids and polymers of monosaccharides, amino acids and nucleotides having a molecular weight greater than 450. Thus, biological molecules include, for example, oligosaccharides and polysaccharides; oligopeptides, polypeptides, and proteins; and oligonucleotides and polynucleotides. Oligonucleotides and polynucleotides include, for example, DNA and RNA.

At page 14, ll. 19-23:

It is emphasized that small molecules can have any molecular weight. They are merely called small molecules because they typically have molecular weights less than 450. Small molecules include compounds that are found in nature as well as synthetic compounds. The [Preferably, the] small molecules of the present invention inhibit the growth of refractory tumor cells that express EGFR/HER1 tyrosine kinase.

At page 15, lines 14-16

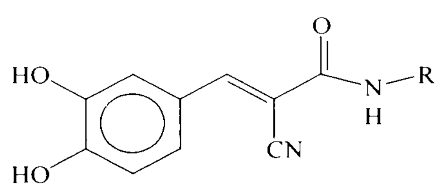
Fry et al., Science 265, 1093-1095 (1994) discloses a compound, PD 153035, having a structure that inhibits EGFR. The structure of PD 153035 is shown below: [in Figure 1. The compound shown in Figure 1 of the Fry et al. article is incorporated herein by reference.]



PD 153035

At page 15, lines 17-19

Osherov et al., J. Biol. Chem., 268, 11,134-142 (1993), disclose tyrphostins that inhibit EGFR/HER1 and HER2. The benzylidene malononitrile or tyrphostin compounds disclosed in the Osherov et al. article, and, in particular, those in Tables I, II, III, and IV are incorporated herein by reference and are set forth generically in the following structure:



wherein R is a cyclohexane, benzene, or benzene alkyl having 1-4 carbons in the alkyl, which benzene can be optionally substituted with Cl, OH, or CH_3.

In the Abstract:

A method of inhibiting the growth of refractory tumors that has failed or been resistant to treatment [are stimulated by a ligand of epidermal growth factor in human patients,] comprising administering to a [treating the] human [patients with an effective amount of] an epidermal growth factory receptor (EGFR) antagonist, wherein administration is effective to inhibit growth of the refractory tumor.

PENDING CLAIMS (AS OF DECEMBER 21, 2001)

36. A method of inhibiting growth of a refractory tumor that has failed or been resistant to treatment comprising administering to a human an epidermal growth factor receptor (EGFR) antagonist and a chemotherapeutic agent, wherein administration is effective to inhibit growth of the refractory tumor.

37. The method according to claim 36, wherein the refractory tumor overexpresses EGFR.

38. The method according to claim 36, wherein the refractory tumor is a refractory tumor of the breast, heart, lung, small intestine, colon, spleen, kidney, bladder, head and neck, ovary, prostate, brain, pancreas, skin, bone, bone marrow, blood, thymus, uterus, testicles, cervix, or liver.

39. The method according to claim 36, wherein the refractory tumor is a refractory tumor of the colon or head and neck.

40. The method according to claim 36, wherein the refractory tumor is a refractory squamous cell tumor.

41. The method according to claim 36, wherein the EGFR antagonist is administered intravenously.

42. The method according to claim 36, wherein the EGFR antagonist is administered orally.

43. The method according to claim 36, wherein the EGFR antagonist is administered at a dose of about 10 to about 500 mg/m^2 weekly.

44. The method according to claim 36, wherein the EGFR antagonist inhibits stimulation of EGFR by its ligand.

45. The method according to claim 44, wherein the EGFR antagonist inhibits binding of EGFR to its ligand.

46. The method according to claim 44, wherein the EGFR antagonist binds EGFR externally.

47. The method according to claim 44, wherein the EGFR antagonist binds EGFR internally.

48. The method according to claim 44, wherein the EGFR antagonist inhibits binding of ATP to EGFR.

49. The method according to claim 44, wherein the EGFR antagonist competes with ATP for EGFR.

50. The method according to claim 44, wherein the EGFR antagonist inhibits EGFR phosphorylation.

51. The method according to claim 44, wherein the EGFR antagonist inhibits EGFR tyrosine kinase activity.

52. The method according to claim 36, wherein the EGFR antagonist comprises an antibody, or functional equivalent thereof, specific for EGFR.

53. The method according to claim 52, wherein the antibody comprises a constant region of a human antibody.

54. The method according to claim 53, wherein the antibody is a chimeric antibody comprising a variable region of a mouse antibody.

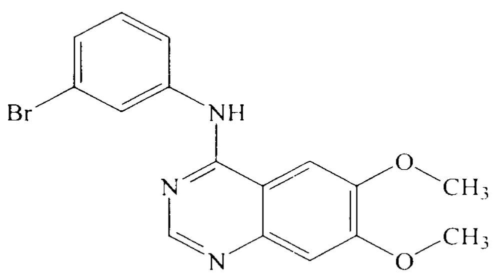
55. The method according to claim 53, wherein the antibody is a humanized antibody comprising a variable region having complementarity-determining regions (CDRs) of a mouse antibody and framework regions of a human antibody.

56. The method according to claim 53, wherein the antibody is a human antibody comprising a variable region of a human antibody.

57. The method according to claim 53, wherein the antibody is administered at a dose sufficient to saturate EGFR.

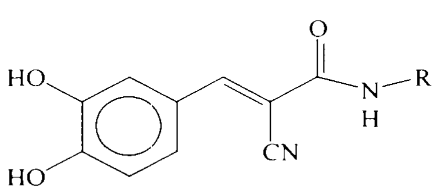
58. The method according to claim 36, wherein the EGFR antagonist comprises a small molecule.

59. The method according to claim 58, wherein the small molecule comprises a compound, PD 153035, having the following structure:



60. The method according to claim 58, wherein the small molecule comprises a benzylidene malononitrile or tyrphostin compound.

61. The method according to claim 60, wherein the benzylidene malononitrile compound comprises the following structure:

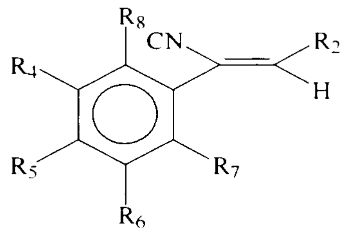


wherein R is a cyclohexane, benzene, or benzene alkyl having 1-4 carbons in the alkyl, which benzene can be optionally substituted with Cl, OH, or CH_3.

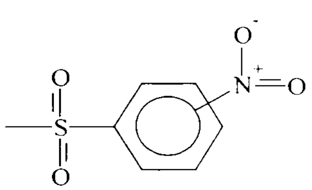
62. The method according to claim 60, wherein the small molecule comprises a styryl substituted heteroaryl compound.

63. The method according to claim 62, wherein the styryl substituted heteroaryl compound comprises a monocyclic ring with 1 or 2 heteroatoms or a bicyclic ring with from 1 to about 4 heteroatoms, which can be optionally substituted or polysubstituted.

64. The method according to claim 62, wherein the styryl substituted heteroaryl compound comprises the following structure:



wherein R is H, alkyl, or aralkyl; R_2 is an about 8- to about 12-membered bicyclic aryl ring including 1 to about 4 N, O or S atoms or 1 to about 4 N-oxide groups, which ring can be optionally substituted with 1 to about 3 R_9 substituents having no common points of attachment to said ring; R_4, R_5, R_6, R_7, and R_8 are each independently H, CN, alkyl, halo, OR, CHO, COOH, NRR or an N-oxide thereof, NO_2, $NHCOCH_3$, SR, CF_3, CH=CHCOOH, $CHCO(CH_2)_2COOH$, heterocyclic, heteroaryl, or the following structure:

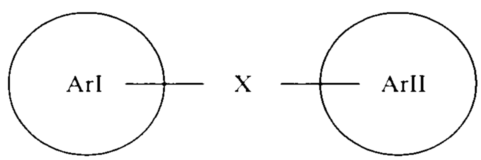


65. The method according to claim 58, wherein the small molecule comprises a tricyclic pyrimidine compound.

66. The method according to claim 65, wherein the tricyclic pyrimidine compound comprises a 4-(3-bromoanilino)benzothieno[3,2-d]pyrimidine; 4-(3-bromoanilino)-8-nitrobenzothieno[3,2-d]pyrimindine; 8-amino-4-(3-bromoanilino)benzothieno[3,2-d]pyrimidinel or 4-(3-bromoanilino)-8-methoxybenzothieno[3,2-d]pyrimidine.

67. The method according to claim 58, wherein the small molecule comprises a bis mono or bicyclic aryl, heteroaryl, carbocyclic, or heterocarbocyclic compound.

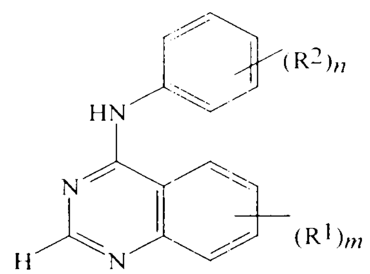
68. The method according to claim 58, wherein the small molecule comprises a compound having the following structure:



wherein ArI and ArII are independently a substituted or unsubstituted mono- or bicyclic ring, said rings optionally substituted with 1 to about 3 R groups; X is $(CHR_1)_{0\text{-}4}$ or $(CHR_1)_m$-Z-$(CHR_1)_n$, which Z is O, NR', S, SO, or SO_2, m and n are 0-3 and $m+n$=0-3 and R_1 and R' are independently H or alkyl, or a pharmaceutically acceptable salt thereof.

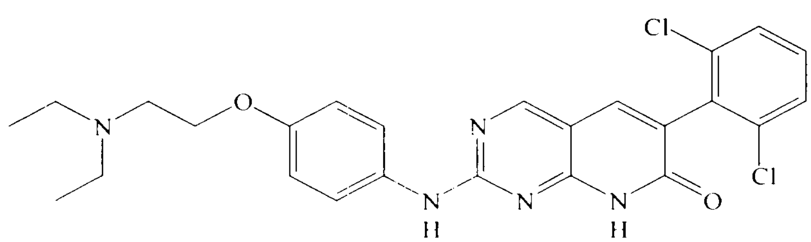
69. The method according to claim 58, wherein the small molecule comprises a quinazoline derivative.

70. The method according to claim 69, wherein the quinazoline derivative comprises a compound having the following structure:



wherein m is 1, 2 or 3 and each R^1 includes hydroxy, amino, carboxy, carbamoyl, ureido, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, hydroxyamino, (1-4C)alkoxyamino, (2-4C)alkanoyloxyamino, trifluoromethoxy, (1-4C)alkyl, (1-4C)alkoxy and (1-3C)alkylenedioxy and n is 1 or 2 and each R^2 includes hydrogen, hydroxy, halogeno, trifluoromethyl, amino, nitro, cyano and (1-4C)alkyl; or a pharmaceutically acceptable salt thereof.

71. The method according to claim 58, wherein the small molecule comprises a compound, PD 166285, having the following structure:



72. The method according to claim 36, wherein the method further comprises administering an adjuvant.